

## REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-9, and 11-47 are pending in this application.

### I. CLAIM REJECTIONS UNDER 35 USC §112

Applicants thank the Examiner for withdrawing the rejection of Claims 15-28 under 35 U.S.C. §112, second paragraph.

### II. CLAIM REJECTIONS UNDER 35 USC §102

Applicants thank the Examiner for withdrawing the rejection of Claims 15 and 20-27 under 35 U.S.C. §102 as being anticipated by Jones et al. *Macromolecules*, 2000, Vol. 33, p. 8301-8306 ("the Jones Reference").

### III. CLAIM REJECTIONS UNDER 35 USC §103

#### A. Claims 1-9 and 11-28 over Jones in view of Kurisawa, in further view of Cai

The Examiner has rejected Claims 1-9 and 11-28 under 35 U.S.C. 103(a) as being unpatentable over the Jones Reference in view of Kurisawa et al. *Journal of Controlled Release*, 1998, Vol. 54, p. 191-200 ("the Kurisawa Reference") and further in view of over Cai et al. *Journal of Applied Polymer Science*, 2002, Vol. 83, p.169-178 ("the Cai Reference").

The Examiner states that the Jones Reference teaches a method of preparing an interpenetrating polymer network (IPN) of nanoparticles (p. 6 of the Office Action mailed 12.9.09), and that the IPN is prepared using many of the same steps as recited in the current claims.

Applicants respectfully disagree with the Examiner's assessment. The Jones Reference teaches preparation of core-shell hydrogel nanoparticles (Title; abstract; p. 8301, column 2, third paragraph; p. 8302, column 1, sixth paragraph; Figures 1, 2, 4, 5, and 6; Scheme 1; and p. 8305, column 1, last paragraph). These nanoparticles of Jones have a distinct core phase, and a distinct

shell phase, with an interface between the two. *See* Figure 1, on page 8302, of the Jones Reference. The Jones Reference teaches, “(t)hese images also suggest that **the interface between the two materials is fairly sharp and not highly interpenetrated.**” (p. 8302, column 1, sixth paragraph). Therefore, the reference **does not** teach an *interpenetrating* polymer network of nanoparticles.

The overall chemical composition of core-shell particles and of IPN nanoparticles **maybe** similar, but the structures are different. As a result, the dispersion of core-shell particles does not have the inverse thermoreversible gelation as the dispersion of the IPN particles does. As an example, both graphite and diamond have the same composition (that is, they are composed of exactly the same carbon (C)), but one cannot say that graphite and diamond are the same thing. Graphite is very soft but diamonds are the hardest known natural substance. This is because they have different structures. The Examiner has stated that the Jones Reference also teaches an aqueous dispersion of hydrogel nanoparticles comprising an interpenetrating polymer network (p. 7 of the Office Action mailed 12.9.09), comprising many of the same components as recited in the current claims.

Applicants respectfully submit that, as described above, **the Jones Reference does not teach an interpenetrating polymer network of nanoparticles, rather, it teaches core-shell nanoparticles having an interface between the two.** (*See* Title; abstract; p. 8301, column 2, third paragraph; p. 8302, column 1, sixth paragraph; Figures 1, 2, 4, 5, and 6; Scheme 1; and p. 8305, column 1, last paragraph).

The Examiner goes on to state that the Jones Reference teaches that at 70° C polymerization temperature, polymer interpenetration was low and that polymerization inside the nanoparticles can be hindered, and that a person of ordinary skill in the art would therefore have recognized that there is a problem with increased temperature (i.e. lack of interpenetration).

Applicants respectfully disagree with this assessment. The Jones Reference teaches that, “...**shell polymerization inside the core particles is sterically hindered due to the high density of the globular core at 70° C.**” (p. 8302, column 1, sixth paragraph). Therefore, **it is the high density of the core, and not the temperature, which is cited as the reason for the lack of interpenetration.** There is no specific teaching relating to the effect of temperature on interpenetration in the cited references. There is **no** teaching in the Jones Reference which would

have led one of skill in the art to lower the polymerization temperature for the shell polymer in an effort to produce an interpenetrating polymer network hydrogel.

The Title of the Jones Reference says: “Synthesis and Characterization of Multiresponsive **Core-Shell Migrogels** [Emphasis added].” The Experimental Section of the Jones Reference contains a section on: “Preparation of **Core-Shell Hydrogel Nanoparticles**. [Emphasis added].” *See*, p. 8301, second column, second full paragraph. The core-shell nanoparticles of the Jones Reference always disperse in water **regardless of the temperature**. The mixture flows as a fluid, there is **no gelation** temperature in the Jones Reference. As discussed below, this is different from the IPN nanoparticles of the present invention. The “state” of the IPN nanoparticles of the present invention is temperature dependent. Figure 12 of the current patent application shows the temperature dependent viscosity of aqueous dispersions of IPN155 nanoparticles at different polymer concentrations. That is, when the system was heated to above the gelation temperature  $T_g$  (about 34 °C), it underwent a transformation from a low-viscous fluid to a gel.

If anything, the teaching of the Jones Reference about “**core-shell hydrogel nanoparticles**” is the **antithesis** of the present claims which recite “**interpenetrating polymer network (“IPN”) nanoparticles** and that the IPN nanoparticles are **substantially free of a core-shell polymer configuration**.” *See* Claims 1, 29, and 41. The Jones Reference actually **teaches away** from the present invention.

The Examiner states that the Kurisawa Reference teaches IPN-structured hydrogels prepared below the transition temperature of one of the components (gelatin), and that this composition had increased miscibility and a dual stimuli-responsive degradation. However, the dual stimuli-responsive degradation of the Kurisawa Reference is **an enzymatic degradation** promoted by the addition of  $\alpha$ -chymotrypsin or dextranase (p. 199, second column, last paragraph), and is therefore entirely distinct from the **reversible gelation in response to a change in stimulus applied thereon** as recited in the current claims. Enzymatic degradation would not be expected to be reversible, and

is an entirely different physical process from the gelation of the current claims. Therefore, a person of skill in the art would not rely on the teachings of the Kurisawa for guidance in producing an IPN hydrogel which exhibits a reversible gelation in response to a change in temperature.

Further, the “**sol-gel transition temperature**” of gelatin referred to by the Examiner is different from the “**the gelation temperature**” recited in the current claims.

At a temperature below the “sol-gel transition temperature” of the Kurisawa Reference, the gelatin exists in a “frozen” state, while at a temperature above this “sol-gel transition temperature,” the gelatin exists in a “melted” state.

In contrast, at a temperature below the “the gelation temperature” recited in the current claims, the IPN nanoparticles disperse uniformly in water and flow like a fluid. At a temperature above the “gelation temperature,” the IPN nanoparticles stick together to form a solid gel.

For example, Fig. 6 of the present application shows that below  $\approx 34^{\circ}$  (the gelation temperature), the dispersion was a fluid (it could flow as the test tube was tilted); while above  $\approx 34^{\circ}$  (the gelation temperature), the dispersion became a solid (it could not flow even the test tube was turned upside down). This direct observation was further quantified with viscosity measurements as shown in Figure 12.

The Examiner states that the Jones Reference teaches that in core-shell systems, one polymer has a chemical or mechanical influence over the swelling of the other polymeric component. This is not relevant to the current claims, **which recite nanoparticles of interpenetrating polymer networks instead of core-shell systems**. As discussed above, the teaching of the Jones Reference is the antithesis of the present claims. The Jones Reference teaches away from the present invention.

The Examiner states that the Cai Reference teaches that inside IPN hydrogels, each network may retain its own properties, and the combined properties of the IPNs can be controlled by the ratios of their component monomers. However, this does not offer any guidance regarding what “combined properties” are, and which changes in ratio would have a given effect.

The Examiner concludes that a person of ordinary skill in the art at the time the invention was made, recognizing that high polymerization temperatures can hinder the polymer interpenetration and that phase morphology in the IPN-structured hydrogels was varied with the preparation temperature, would have been motivated to modify the method and composition as

taught by Jones et al. by optimizing and lowering the temperature according to the teachings of the Jones Reference in order to provide a method of preparing a dispersion of hydrogel nanoparticles with a reasonable expectation of forming a high polymer interpenetration.

As described above, the Jones Reference does **not** refer to an interpenetrating polymer network of nanoparticles, and in fact teaches core-shell nanoparticles having an interface between the two (p. 8302, column 1, sixth paragraph). Moreover, the Jones Reference states that the “shell polymerization inside the core particles is **sterically hindered** due to the **high density** of the globular core at 70° C.” See p. 8302, first column, the 6<sup>th</sup> paragraph. Thus, it is the high density, and not the temperature, as the reason for the lack of interpenetration. Therefore, one of skill in the art would not have been motivated to make these modifications.

The Examiner concludes that one of skill in the art would have been motivated to further modify the method of the Jones Reference by adding a drug at a third temperature below gelation temperature according to the teachings of the Kurisawa Reference. In fact, one of skill in the art would have been discouraged from adding any drug to a hydrogel by the teachings of the Kurisawa Reference, which read, in part, ““hydrogels are not suitable for regulated release of low molecular weight- and water-soluble drugs.” (p. 192, second column, second paragraph). Therefore, the Kurisawa Reference also **teaches away** from the present invention.

Therefore, one of skill in the art would not have been motivated by the Jones Reference, the Kurisawa Reference, or the Cai Reference, or any combination thereof, to practice the method or composition of current Claims 1-9 and 11-28. Combining references that teach away from the claimed subject matter would not have rendered the claimed subject matter obvious.

**B. Claims 29-47 over Cai in view of Jones, in further view of Hennink & Nostrum**

The Examiner has rejected Claims 29-47 over the Cai Reference, in view of the Jones Reference, and in further view of Hennink and Nostrum *Advanced Drug Delivery Reviews*, 2002, Vol. 54, p. 13-36 (“the Hennink Reference”).

The Examiner has stated that the Cai Reference teaches a method of preparing a nanocluster of cross-linked nanoparticles (p. 12 of the Office Action mailed 12.8.09). Applicants respectfully disagree with this statement. The Cai Reference teaches “**bulk hydrogels with microstructure**

(BHMs),” rather than nanoparticles (Abstract; p. 171, column 1, paragraph 2; p. 171, column 2, paragraph 3). The BHMs are formed from microgel particles which have been cross-linked to form a bulk hydrogel which can be cut into disk form and handled (p. 171, column 2, paragraph 3).

As the Examiner has pointed out, the Cai Reference teaches that, “NIPAAm-AA microgels are ionic particles because of the carboxylic charge on AA. In these microgel particles, the AA groups tend to lie on the surface of the particles, and NIPAAm groups lie toward the inside...(i)n this conformation, the carboxyl groups on the microgel particle surface can also be further cross-linked under suitable conditions forming interpenetrating network structures.” (p. 172, column 2, last paragraph – p. 173, column 1, first paragraph). Therefore the bulk hydrogels of the Cai Reference are formed from microparticles which have a core (NIPAAm) and shell (AA) component, and which are cross-linked to one another. These bulk hydrogels are therefore clearly distinct from the present nanoclusters of cross-linked interpenetrating polymer network (“IPN”) nanoparticles, comprising: at least two IPN nanoparticles linked by a cross-linking group.

The Examiner states that, while the Cai Reference does not teach a dispersion of IPN nanoparticles, the Jones Reference teaches an aqueous dispersion of nanoparticles (p. 12 of the Office Action mailed 12.8.09).

Applicants respectfully disagree with the Examiner’s assessment. As described in detail above, the Jones Reference **teaches away from the current invention**, the reference teaches core-shell hydrogel nanoparticles, which are distinct from the currently claimed IPN nanoparticles. The current claims specifically recite IPN nanoparticles which are substantially free from a shell and core polymer configuration.

Moreover, as previously described, neither the Cai Reference and the Jones Reference discloses either the step of cooling the reaction mixture to a second temperature below the low critical solution temperature of the first monodispersed polymer, or an aqueous dispersion which exhibits a change in particle size of less than 30 nm when the aqueous dispersion is heated from below a volume phase transition temperature to above a volume phase transition temperature at a concentration of  $2.88 \times 10^{-5}$  g/ml. Therefore, these references would not have suggested or motivated one of skill in the art to practice the invention recited in the amended claims.

The Examiner has stated that the Hennink Reference teaches cross-linking agents for cross-linking water-soluble polymers with amide bonds. Applicants submit that there is no teaching in Hennink which would have motivated one of skill in the art to practice the currently-claimed method or to produce the currently-claimed composition which comprises nanoclusters composing of a two or more interpenetrating polymer network nanoparticles.

The Examiner concludes that a person of ordinary skill in the art at the time the invention was made would have been motivated to try and use the cross-linking agents of the Hennink Reference to cross-link the dispersion of IPN nanoparticles. As noted above, the Cai Reference does not teach a dispersion of IPN nanoparticles, but rather teaches core-shell hydrogel nanoparticles. Therefore, there is no teaching in the Cai Reference, the Jones Reference, the Hennink Reference, or any combination of the references, which would have motivated one of skill in the art to practice current Claims 29-47.

In summary, combination of the Cai Reference, the Jones Reference, the Hennink Reference can't produce the claimed invention shown in Figures 6, 12, and 21.

#### IV. Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

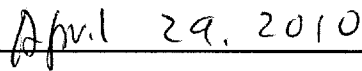
If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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